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Staphylococcal Infections

DAVID E. ROGERS

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Staphylococcal Infections

DAVID E. ROGERS

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INFECTIONS causing serious therapeutic problems in hospitals today are different from those of 20 years ago. Before the development of effective antimicrobial drugs, acute bacterial infections caused by pneumococci, streptococci and meningococci ranked high as a cause of morbidity and mortality. These bacterial diseases were characteristically dramatic in onset, and the outcome was determined in a relatively short time. Either the patient died or the infection was controlled by the host. Although these bacteria were maintained in human reservoirs, pathogenic strains were not carried by most normal people. Infection of apparently healthy persons was common and thought to be acquired from external sources.

As these acute infections have come under effective control, certain others of a different nature have become increasingly important. Recently infections caused by staphylococci seem to be on the increase in hospitals throughout the world. Infections due to certain enteric bacilli and fungi also are common in hospitalized patients.

These infections, in contrast to acute bacterial infections, are caused by microorganisms residing in the normal human host. All tend to follow a chronic, relapsing course; all tend to produce local, destructive, focalizing lesions. Humoral immunity in the classic sense does not arise during infection. Most important, perhaps, are indications that these micro-

organisms require marked alterations in human-host susceptibility before active invasion and clinical disease can occur.

In prolonging the life span of many patients with serious disease, we seem to create a group highly vulnerable to infection. Such drugs as the adrenal steroids, corticotropins, nitrogen mustards or the folic-acid antagonists are thought to alter host-defense mechanisms. Advances in thoracic and abdominal surgery and increased use of prolonged intravenous therapy through cutdowns on indwelling venous catheters open

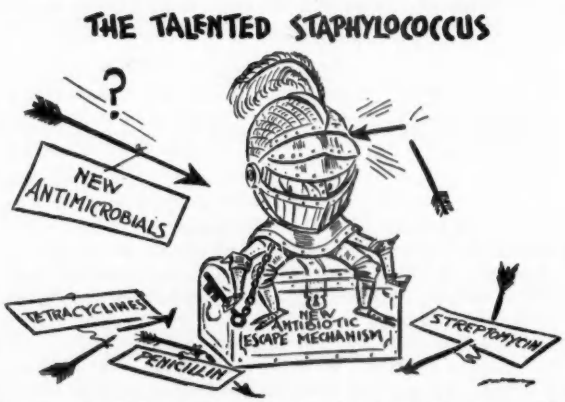

FIG. 1.—Staphylococci are hardy parasites. They have demonstrated the ability to emerge resistant to every new antistaphylococcal drug placed in use.

many new avenues for microorganisms. In this setting, staphylococcal infections are common.

Certain characteristics of staphylococci help to create this situation. These are:

1. The almost universal presence of potentially pathogenic staphylococci in normal human beings.
2. The capacity of staphylococci to become resistant to almost every new antimicrobial agent.
3. The heavy reservoir of antibiotic-resistant staphylococci that develop in many hospitals where seriously ill patients are congregated.
4. The tendency of staphylococci to produce disease in patients already seriously debilitated.

With certain exceptions, to be discussed, there is little evidence to suggest that the strains of staphylococci currently prevalent are more invasive than were those of 20 years ago. Nevertheless, hospitalized patients in whom staphylococcal infections now commonly develop often have other critical diseases. When staphylococcal infections develop in these patients, mortality is high. Current therapy is unsatisfactory.

This monograph is not intended as a substitute for the excellent chapters on staphylococcal infections to be found in current medical textbooks. Because of the unsatisfactory nature of therapy and the changes in thinking which are necessary with each new development, certain basic aspects of the staphylococcal-host relationship which may bear on the character of staphylococcal infections are considered in detail. Currently important clinical syndromes produced by staphylococci are emphasized, whereas less significant staphylococcal infections are but briefly noted. Basic principles of therapy in staphylococcal infections are stressed. The antibiotic regimens in current use (late 1957) are outlined, recognizing that therapy should and must change as patterns of antimicrobial resistance change and as newer antibiotics become available.

It is clear that staphylococcal infections, once established, will continue to cause high mortality and that we are approaching an era in which prevention of staphylococcal infections must assume greater importance. Despite immense gaps in our epidemiologic knowledge, a tentative program for preventing staphylococcal disease has been arbitrarily set up, using information currently available.

BIOLOGIC CHARACTERISTICS OF STAPHYLOCOCCI

Certain biologic characteristics of pathogenic strains of staphylococci may offer important clues to the pathogenesis of staphylococcal infections. These include:

1. The hardy and adaptable nature of pathogenic staphylococci (Fig. 1).
2. The exotoxin produced by many strains of staphylococci.
3. Production of the enzyme, staphylocoagulase.
4. The ability of pathogenic strains of staphylococci to survive within human phagocytic cells.
5. The nature of the local abscess lesion characteristically produced by staphylococci.

THE HARDY STAPHYLOCOCCUS.—Most bacteria pathogenic for man have precise nutritional requirements and die rap-

idly when removed from the human host. In contrast, pathogenic strains of staphylococci survive outside the host for long periods. Staphylococci grow on a wide variety of simple media; they can withstand higher temperatures than most bacteria and survive in relatively dry atmospheres. Numerous studies have shown that living staphylococci are found in lint, dust and the interstices of blankets, mattresses and linens. It has been demonstrated that many staphylococci disseminate as aerosols where blankets are shaken or where pillows or mattresses are handled. Simple laundering of linens and blankets at average washing temperatures does not eliminate pathogenic staphylococci. These facts are important in the maintenance of staphylococci within hospitals.

STAPHYLOCOCCAL EXOTOXIN.—During growth, an extracellular exotoxin is produced by many strains of staphylococci. When exotoxin is injected into the skin of experimental animals, striking dermal necrosis takes place. Evidence suggests that exotoxin may play an important role in certain human infections. Occasionally, staphylococcal bacteremia may run a fulminant clinical course resembling the experimental illness produced by intravenous injection of exotoxin in animals. Certain patients with cutaneous staphylococcal infections develop extensive necrosis of the skin and subcutaneous tissues. This appears to be due to local production of dermatonecrotic exotoxin by rapidly multiplying staphylococci.

STAPHYLOCOAGULASE.—The major staphylococcal strains producing human infection elaborate an enzyme, coagulase, which causes clotting of human and certain animal plasmas in vitro. Experiments show that the action of coagulase requires the presence of a serum globulin closely related to, or perhaps a portion of, the prothrombin molecule for conversion of fibrinogen into fibrin.

This uncommon biologic characteristic and the high degree of correlation between coagulase production and human pathogenicity suggest that coagulase may play a part in the production or perpetuation of staphylococcal infections. In the 1940's Hale and Smith suggested that coagulase might protect the staphylococci from phagocytosis through the creation of a fibrin envelope about clumps of microorganisms that would not allow leukocytes to ingest them (1). Nevertheless, it has been shown that a fibrin clot forms an ideal framework on which surface phagocytosis can take place (2). Also, it can be shown that staphylococci are avidly ingested by both human and animal leukocytes in the presence of

fibrin, even under conditions in which pneumococci, streptococci or other virulent bacteria are rarely phagocyted (3).

Recent studies by Ekstedt indicate that coagulase may allow staphylococci to grow readily in human or animal sera. In the absence of coagulase, staphylococci appear to multiply slowly, if at all (4).

That coagulase may allow staphylococci to multiply rapidly within a few hours following invasion seems the most acceptable theory yet advanced to explain the role of coagulase. Current evidence suggests that events of the first few hours following bacterial invasion of tissues are critical in deciding whether active infection or eradication of the parasite will occur. Any mechanism that may give staphylococci an initial advantage may be all important in establishing disease.

INTRACELLULAR SURVIVAL OF STAPHYLOCOCCI.—In contrast to pneumococci or streptococci, pathogenic staphylococci are able to survive within polymorphonuclear leukocytes (3). Recent studies indicate that they multiply within the cytoplasm of phagocytes, eventually causing death and dissolution of the host cell (5).

Saprophytic strains of staphylococci are promptly destroyed by phagocytosis. Studies of the behavior of staphylococci injected into the blood stream of rabbits indicate that living staphylococci are swiftly incorporated within circulating leukocytes and thus may be protected from being trapped within the reticuloendothelial system of the liver and spleen (6). These intracellular staphylococci have been shown to circulate in the blood stream for long periods. Such leukocytes may lodge in distant foci and staphylococci contained within their cytoplasm thus may set up metastatic foci of infection. Intracellular residence also may protect microorganisms from certain antimicrobial substances present in extracellular fluids.

THE STAPHYLOCOCCAL ABSCESS.—The staphylococcal abscess consists of a necrotic central core of dead and dying leukocytes and bacteria. Probably only staphylococci around the periphery of the abscess are viable, and they are surrounded by a relatively avascular wall of fibrin and fibrous tissue. Microbes remain constant at levels of 100 million to 1 billion per ml. within established abscess cavities. It is probable that staphylococci multiply sluggishly, if at all, inside such lesions.

Staphylococci harbored in such walled-off lesions are virtually external to the host. Likely they are protected in such sites from host mechanisms operating in better perfused tis-

sues. Virtually all of the microorganisms producing infections that tend to pursue long relapsing courses (tubercle bacilli, fungi, brucella, salmonella) produce such focal necrotic or granulomatous lesions.

The abscess per se has been advanced as a reason for the chronic, relapsing nature of staphylococcal infections, for the lack of any clearcut humoral-immune response and for the common failure of antibiotics to affect abscess cavities. These concepts bear examination.

The "externalization" of staphylococci in local lesions may influence immune response. It has been shown that a fibrin membrane can operate as a selective filter, allowing only certain protein molecules and dyes to pass. It is possible that important antigenic components of the staphylococcus inside the abscesses fail to pass to the systemic circulation in sufficient quantity to operate as effective antigenic stimuli.

It is commonly stated that therapeutic failures occur because antimicrobial drugs do not penetrate the interior of local staphylococcal abscesses. Unpublished studies within our laboratory show that this may not be the case. It can be shown that penicillin rapidly appears within the interior of avascular fibrous cavities and persists in concentrations equaling those in the serum. Other current studies suggest that staphylococci as they exist in abscess lesions are "physiologically insusceptible" to antimicrobials. It is clear that this is partly due to the sluggish growth of microorganisms in established lesions. Most antibiotics do not affect microorganisms that are not actively multiplying. Whether other factors also tend to prevent antibiotic action against microorganisms in abscesses remains to be determined.

EPIDEMIOLOGY OF STAPHYLOCOCCAL INFECTIONS

Pathogenic staphylococci are harbored by 20–50% of normal, nonhospitalized people. Mucous membranes of the anterior nares are the common carrier site. The skin on the back of the hand, the back of the neck, upper back and the axillae are common sites where staphylococcus reside. Some persons are only occasional transient carriers of virulent staphylococci. Approximately 20% of normal people are persistent carriers, often harboring a single phage type of staphylococcus for many months to years.

Epidemiologic studies show that more than 90% of newborn babies in nurseries acquire staphylococci in the anterior

nares within their first 2 weeks (7, 8). Likely such colonization results from inhalation of air-borne staphylococci in dust, lint and droplet nuclei. Coagulase-positive staphylococci are numerous in air samples from hospital wards, operating rooms and nursery units. The human nose acts as a screen for air-borne particles. Thus staphylococci of potential virulence are repeatedly seeding the anterior nares. In many cases these are promptly eliminated. It is thought that the persistent state ensues when impinged staphylococci gain a more permanent foothold. The skin-carrier state generally follows the appearance of staphylococci in the nose.

Current evidence suggests that many staphylococcal infections arising in a community are self-inflicted; that is, staphylococci are transferred to skin abrasions or wounds from the anterior nares. Within hospitals, it appears that many infections are initiated from without by air-borne staphylococci harbored by other patients and hospital personnel.

The Problem of Antimicrobial-Resistant Staphylococci

The capacity of pathogenic strains of staphylococci to emerge resistant to every new antibiotic complicates the epidemiology of staphylococcal infections and tends to create large reservoirs of pathogenic, antimicrobial-resistant staphylococci in hospitals.

Studies on the penicillin sensitivity of staphylococcal strains isolated from 1942–1944 indicate that only an occasional strain was not susceptible to penicillin. The incidence of strains resistant to penicillin has risen steadily in all subsequent studies, and now ranges between 60 and 80% of strains isolated in most hospitals. Spink has shown that the *degree* of penicillin resistance also has increased (9). As far back as 1940, occasional strains were found to be resistant to 1 unit of penicillin per ml., but rarely resistant to more than 25 units. It is now common to find strains within a hospital able to grow in 50 to 500 units of penicillin per ml. Epidemiologic studies by Lepper and his associates show that resistant strains of staphylococci rapidly emerge when a new antistaphylococcal drug is put in general use (10).

It is now common to find within hospitals strains of staphylococci highly resistant to penicillin, streptomycin and the tetracyclines. It is currently less common to isolate strains resistant to erythromycin, chloramphenicol, or novobiocin—

all antibiotic agents of relatively recent origin and less widespread use.

It is important to note that the studies mentioned are from hospitals. The phenomenon of drug resistance has, until recently, been primarily a hospital problem. Further, most large-scale observations on antibiotic resistance have been carried out in normal people who are carriers of staphylococci, not patients with staphylococcal infections.

Figure 2 is based on published observations made on staph-

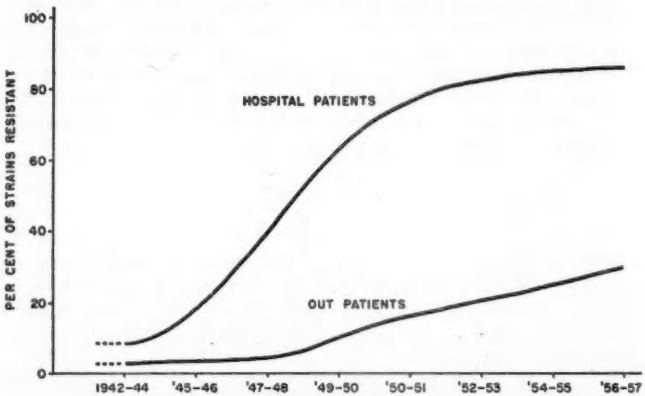

FIG. 2.—Incidence of strains of staphylococci resistant to penicillin has risen steadily in hospitalized persons. A later, lesser increase in the number of resistant strains has been apparent in people without hospital contact.

ylococcal carriers from 1942–1956 in the United States, England, Australia and Canada. It shows that the number of isolates resistant to penicillin has risen steadily in hospital patients. In contrast, many strains isolated from the non-hospitalized remain sensitive to penicillin, with a slower rise in resistant strains evident recently.

Table 1 shows that most staphylococcal infections occurring within hospitals are due to strains broadly resistant to antimicrobials, while extrahospital infections are due to susceptible staphylococci. In this study the antimicrobial resistance patterns of strains isolated from 73 patients acquiring infec-

tion within The New York Hospital are contrasted with the resistance of strains isolated from 62 outpatients presenting with established staphylococcal infections. In our outpatients, previous medical therapy is common, and it is likely that a number of these patients had previously been hospitalized or treated elsewhere. Nevertheless, striking differences in staphylococcal resistance patterns are apparent, depending on the setting in which infection arose.

The carrier rate of staphylococci is significantly higher in hospital personnel. Eighty to 95% of doctors, nurses and attendants harbor staphylococci in the anterior nares. In

TABLE 1.—Patterns of Antibiotic Resistance Encountered in Coagulase-Positive Staphylococci Isolated from 135 Infections at The New York Hospital, 1957

Antibiotic	Infection Acquired in the Hospital (73)	Infection Acquired Outside the Hospital (62)
	Per Cent Resistant	Per Cent Resistant
Penicillin	85	51
Streptomycin	63	13
Tetracyclines	66	22
Erythromycin	20	1.5
Chloramphenicol	1	1.5
Novobiocin	5	10
Bacitracin	8	0

many recent studies, 60–75% of these strains have been resistant to a large number of antibiotics.

How has this situation arisen? The work of Knight and his associates shows that the administration of an antistaphylococcal drug significantly increases the chances of the hospitalized patient becoming a carrier of a strain of "hospital" staphylococcus resistant to antibiotics (11). These studies show that patients entering a hospital with an antibiotic-sensitive strain of staphylococci in their nares generally maintain this strain throughout their hospital stay. In contrast, patients receiving either penicillin or a tetracycline during hospitalization tend to become carriers of strains of staphylococci prevalent in the hospital.

These observations help explain how the reservoir of resistant staphylococcus within hospitals has increased. In an atmosphere continuously exposed to antimicrobials, patients and personnel tend to eliminate their antibiotic-sensitive strains of staphylococci. Thus antimicrobial-resistant strains

that survive in hospitals can readily enter this vacuum and induce the carrier state.

These studies do not, however, explain why the carrier rate is so much higher in hospital personnel than in people generally. Two possibilities exist: (1) That resistant strains are better able to survive within the human nose. (That this is unlikely is suggested by the disappearance of the carrier state when the patient leaves the hospital.) (2) That many hospital carriers are transient. This seems more probable. The relatively high concentrations of drug-resistant staphylococci in hospital air indicate that these microorganisms are frequently impinged on the nasal mucous membranes. But this does not necessarily prove that they set up permanent intranasal residence.

Thus the hospital situation into which we admit patients with serious debilitating illnesses presents the very conditions under which transfer of potentially virulent staphylococci is most likely to take place.

FACTORS FAVORING SUSCEPTIBILITY TO STAPHYLOCOCCAL INFECTION

Predisposing Clinical Conditions

Incredibly little is known of the specific factors influencing host susceptibility to staphylococcal disease. Nevertheless, certain clinical conditions are known to predispose to active staphylococcal infection. Loss of skin continuity seems to be an important one. Traumatic or operative wounds, exfoliating skin diseases of any etiology tend to increase the incidence of staphylococcal infections. Cutaneous staphylococcal infections are more common in persons who are continually exposed to greasy skin irritants. Diabetics have a significantly higher incidence of staphylococcal infections than do normal people. Although staphylococcal pneumonia can arise as a primary illness in children, staphylococcal pneumonia in adults classically follows influenza. This relation was well illustrated during the 1957 influenza epidemic. Recently we have learned that seriously ill hospitalized patients can acquire staphylococcal pulmonary infections without having had influenza. The administration of broad-spectrum antimicrobials seems to increase the incidence of staphylococcal enterocolitis.

Immune mechanisms.—Whether the human host devel-

ops immunity to staphylococcal infection is not known. There is definite evidence, however, that the type of staphylococcal syndromes changes with age. Infants seem more susceptible to cutaneous staphylococcal infections. The incidence of staphylococcal bacteremia is significantly higher in infants and young children than in adults who characteristically focalize staphylococcal infections. Acute staphylococcal osteomyelitis is a disease of youth, although such bony localization may be due to greater vascularity of epiphyses in young children.

Experimentally, little humoral immunity has been demonstrated. Animals immunized with staphylococci or their derivatives are not protected against death. In humans, repeated crops of boils may occur over many months, sometimes years, with little deviation, despite continuous antigenic exposure.

CLINICAL STAPHYLOCOCCAL INFECTIONS, 1958

Certain syndromes produced by staphylococci remain relatively unchanged in their clinical manifestations or incidence. Some types of staphylococcal infection are less commonly observed than in the past.

There is little evidence of change in the nature or number of cutaneous or subcutaneous infections produced by staphylococci, including simple folliculitis, boils and deep-seated staphylococcal infections of the apocrine glands of the axilla. The neglected carbuncle associated with bacteremia is uncommon and but rarely seen in current hospital practice. Acute staphylococcal osteomyelitis in children is definitely declining, and chronic, relapsing osteomyelitis is no longer seen on orthopedic wards. Acute staphylococcal food poisoning caused by enterotoxin-producing strains of staphylococci continues in small epidemics, mainly where foods stand at room temperatures for long periods prior to ingestion.

Recently certain types of staphylococcal disease have become more important and perhaps more common. Today the serious major disease syndromes caused by staphylococci are:

1. Staphylococcal infections in newborn infants and nursing mothers.
2. Staphylococcal pneumonia.
3. Staphylococcal bacteremia with or without involvement of heart valves.
4. Staphylococcal wound infections.
5. Staphylococcal enterocolitis.

This shift in type of serious staphylococcal infection reflects, in part, a change in the location in which staphylococcal infections arise. Sixty to 70% of staphylococcal infections now develop *within* hospitals or emerge during the immediate posthospitalization period (9, 12). The entire group of infections to be discussed further might thus appropriately be considered as "syndromes of intrahospital staphylococcal infection."

Epidemic Infections in Newborn Infants and Nursing Mothers

Cutaneous staphylococcal infections in newborn infants in nurseries are an increasing clinical problem. Clearly, more infants acquire hospital-induced staphylococcal infections than formerly, and recurrent nursery epidemics have been reported from widely scattered areas of the world. In one hospital unit recently studied, 46% of newborn infants developed staphylococcal infections during their first few weeks (8). Nursing mothers also acquired staphylococcal infections from their infants.

Typically, infants develop a pustular dermatitis, pyoderma neonatorum as a manifestation of staphylococcal infection. In certain infants, bullous cutaneous lesions (bullous impetigo) arise. The umbilical cord stump, groin, and intertriginous areas are common sites of infection. Breast abscesses develop in many infants. Staphylococcal conjunctivitis also occurs during epidemics. In many infants in whom constitutional symptoms are mild, the cutaneous disease remains local. Nevertheless, pneumonia with empyema, bacteremia and infant death are reported in every series.

The pattern of nursery epidemics of staphylococcal infection is relatively uniform, with early detection difficult. The first indications of nursery infection commonly arise outside the hospital. Infants discharged from the hospital 3–14 days previously develop cutaneous staphylococcal infections. In some instances infants show no infection, but the nursing mother develops staphylococcal mastitis or a breast abscess following hospital discharge. As the epidemic proceeds, the time between discharge and the appearance of infection grows progressively shorter. Finally, cases are discovered within the nursery proper. Often such hospital-acquired disease goes unrecognized until intranursery infections appear.

From studies on the rapid rate hospital newborns acquire

staphylococci, it is generally assumed that nursery outbreaks of staphylococcal infection are directly traceable to the nursery—the result of improper aseptic technic. It is discouraging to note that (a) epidemics arise in nurseries managed under optimal aseptic conditions, (b) tightening of aseptic controls does not always affect the course of an epidemic in progress, and (c) the epidemic strain often is not detected in nursery personnel at the time an epidemic is recognized.

Observations of Wysham and his associates help clarify this problem (8). Their studies show that infants per se can maintain and perpetuate an epidemic once a strain of unusual virulence is introduced to the nursery. Transfer from infant to infant occurs, probably through air-borne staphylococci. Often during epidemics, the responsible strain is found in blankets, lint, mattresses and dust from the nursery.

It is interesting to note that a single phage type, (52/42B/81), is responsible for the majority of epidemics (14). This observation strongly suggests that this strain may be uniquely able to perpetuate itself in the human infant whereas other strains are not. Perhaps this is an example of a staphylococcus of altered virulence emerging in the antimicrobial environment.

Puerperal staphylococcal mastitis and breast abscesses in new mothers are thus acquired from the "colonized" infant who may or may not manifest overt staphylococcal infection. Wysham and his associates show that (a) breast abscesses invariably arise only in mothers who nurse infants carrying staphylococci in the nose and throat, (b) that the epidemic strain 52/42B/81 is commonly the cause of this disease, and (c) that infants inject staphylococci into nursing bottles (and probably into lactiferous ducts) during the suckling process (13). In their studies, almost 40% of mothers nursing infants who were carriers of the nursery epidemic strain developed breast abscesses.

Nursery epidemics constitute one of the most distressing problems in staphylococcal disease. A large portion of adult staphylococcal infections occurs in patients seriously ill with other unassociated illness. With present medical knowledge, patients with leukemia, irreversible congestive failure or metastatic malignancy must die of some cause. Staphylococcal infections are a common current cause of death in such adults. In this group, death, although of serious concern, does not constitute the tragedy represented by death of a newborn infant with hospital-acquired staphylococcal sepsis.

Staphylococcal Pneumonia

Staphylococci were responsible for 1–5% of bacterial pneumonia cases before the introduction of antibiotics. Characteristically, this disease was sporadic, occurred in young adults, and commonly followed influenza. Staphylococcal pneumonia has increased following every influenza epidemic. Many cases developed during the 1957 Asian influenza epidemic.

Currently we see a different staphylococcal entity which appropriately might be called the pneumonia of debilitated, hospitalized patients. These two syndromes, the acute, clinically primary staphylococcal pneumonia arising outside the hospital and staphylococcal pneumonia arising within the hospital, in association with other serious disease, will be considered separately.

Clinically primary staphylococcal pneumonia occurs in both infants and young adults. In common with other bacterial infections of the lung, staphylococcal pneumonia usually begins abruptly with a shaking chill. Repeated chills are common. High fever, progressive dyspnea, cyanosis, productive cough and pleural pain follow swiftly. Peripheral vascular collapse may appear early in the illness. Pleural involvement is prompt, and empyema is often present when the patient is first seen. In young infants, the pleural space is penetrated with exceptional rapidity, and staphylococcal pneumonia is the usual cause of pyopneumothorax in this group.

The lung involvement produced by staphylococci is generally patchy and centrally located. On clinical examination, often a patient appears far sicker and more dyspneic than his pulmonary signs suggest. Intense pleural pain, cyanosis, and tachycardia are common. Examination of the chest may reveal patchy areas of rales, the presence of a pleural friction rub or evidence of pleural fluid. Signs of true lobar consolidation are generally lacking. Staphylococci isolated from such cases are usually sensitive to most antistaphylococcal antibiotics.

The fulminant nature of certain staphylococcal pneumonia cases following influenza is graphically described by Chickering and Parks (15), who document an epidemic of *Staphylococcus aureus* pneumonia in 154 soldiers at Camp Jackson during the influenza pandemic of 1918. Despite their youth and vigor, 152 of these young men died, many within 48–96 hours of the onset of symptoms. Epidemics of staphylococcal pneumonia of lesser virulence which followed the influenza

epidemic of 1941 are reported by Finland, Peterson and Strauss (16), and Michael (17).

A clinical entity seen commonly in current practice in the absence of influenza is staphylococcal pneumonia arising in seriously ill hospitalized patients. Patients with advanced cardiac or pulmonary disease, leukemia or other malignancies, or patients in a coma from any cause, may develop staphylococcal pulmonary infections. The disease frequently develops during antimicrobial therapy. Many such pulmonary infections are caused by staphylococci resistant to the common antistaphylococcal antibiotics.

In many of these patients, the pulmonary infection begins insidiously. A progressively rising septic temperature, a moderate cough and increasing respiratory distress may be the only clinical symptoms. Often these symptoms cannot be differentiated from those characterizing the primary illness. Tachypnea, progressive cyanosis and a rising leukocytosis usually occur in the course of pulmonary infection. There is no specific clinical picture by which this illness can be identified. The appearance of any of these symptoms, or signs, in seriously ill patients, particularly those receiving antimicrobials, should suggest staphylococcal pneumonia.

In many instances, pulmonary involvement follows bacteremia arising from staphylococcal infections elsewhere in the body. Infected bed sores, venous cut downs, or infections about indwelling catheters in the bladder are common primary foci. In certain patients, aspiration secondary to coma, vomiting, or heavy sedation may initiate the infection.

Table 2 contrasts the clinical syndrome of staphylococcal pneumonia seen at The New York Hospital during 3 years preceding the advent of antibiotics with that of cases similarly diagnosed during 1955. Striking differences in the clinical entities involved are apparent. Patients seen in the preantimicrobial period were principally young adults. The majority were admitted with an acute pneumonic illness. Although empyema was common and hospitalization prolonged, the majority (70%) survived. In contrast, patients with staphylococcal pneumonia seen in 1955 were generally older, and the majority had other serious debilitating diseases. Staphylococcal pneumonia developed within the hospital in most cases, and all but 1 patient died.

LABORATORY FINDINGS.—Sputum from patients with staphylococcal pneumonia is not characteristic. Usually it contains blood. In some patients the sputum is frankly purulent, re-

TABLE 2.—CHANGING HOST SETTING IN WHICH STAPHYLOCOCCAL PNEUMONIA OCCURS

PRE-ANTIMICROBIAL PERIOD (1933, 1935, 1940)				ANTIMICROBIAL PERIOD (1955)			
Case 1	Age Sex	Clinical Setting	Outcome	Case	Age Sex	Clinical Setting	Outcome
	33F	Septic abortion, bacteremia, pneumonia	D	1	51F	Carcinoma of kidney, metastatic to liver, lungs, lymph nodes. Intestinal obstruction, terminal pneumonia	D
2	26M	Primary pneumonia—empyema	L	2	55F	Acute leukemia, terminal pneumonia	D
3	47M	Primary pneumonia—empyema	L	3	58F	Nephrolithiasis, uremia operation, terminal pneumonia	D
4	39F	Primary pneumonia	L	4	38F	Myelogenous leukemia—splenectomized, terminal pneumonia	D
5	21F	Primary pneumonia—empyema	L	5	36F	Diabetes, nephropathy, uremia, terminal pneumonia	D
6	33F	Skin abscess, bacteremia, pneumonia	D	6	32F	Primary staph. pneumonia	L
7	28M	Primary pneumonia—empyema	L	7	60M	Carcinoma of lung, metastatic to liver, kidney, pancreas, terminal pneumonia	D
8	45M	Rheumatic heart disease, congestive failure, bronchopneumonia and empyema	L	8	79F	Gastric ulcer, pyelonephritis, uremia, ASCVD, bronchopneumonia	D
9	52M	Hand infection, bacteremia, pneumonia	L	9	64F	Diabetes, acidosis, pyelonephritis, uremia, chronic bronchitis, bronchopneumonia	D
10	38F	Primary pneumonia, rheumatic heart disease	D	10	42M	Advanced pulmonary emphysema, respiratory acidosis. O_2 for 2 years, lobectomy, terminal pneumonia	D
				11	72M	Paralysis agitans, bedridden 6 years, admitted with pneumonia	D
				12	34M	RHD, MS, MI, AS, AI. Hufnagel valve, postoperative mediastinitis, pneumonia	D
				13	72M	Erythema multiforme bullosum, pyelonephritis, uremia, ACTH, undiagnosed pneumonia	D
Average age = 36.2			Mortality = 30%	Average age = 53.4			Mortality = 92.3%

(From Rogers, D. E.: The current problem of staphylococcal infections, Ant. Int. Med. 45:748, 1956.)

sembling the contents of a furuncle. Examination of Gram-stained smears commonly shows masses of polymorphonuclear leukocytes, red blood cells and clusters of large, densely stained cocci. Staphylococci cannot be differentiated readily from other Gram-positive cocci on smears. Nevertheless, finding numerous cocci within the cytoplasm of polymorphonuclear leukocytes strongly suggests the correct diagnosis. Sputum cultures commonly reveal a relatively pure growth of coagulase-positive staphylococci. The white blood-cell count usually exceeds 10,000, with a marked increase in immature granulocyte forms. Occasional patients show an initial leuko-

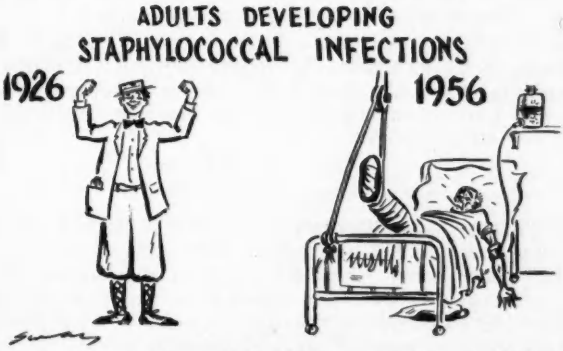

FIG. 3.—Before the antimicrobial era, serious staphylococcal infections were seen primarily in young adults. Today, most of these infections are seen in older hospitalized people.

penia. Blood cultures are positive in less than 15–20% of cases. Indeed, a positive blood culture is sufficiently uncommon in primary staphylococcal pneumonia to suggest that the lung involvement is secondary, and a search for other foci of infection is indicated.

Prognosis.—Prior to antimicrobial drugs, death occurred in 50 to 95% of patients with staphylococcal pneumonia. The presence of bacteremia was almost invariably associated with death.

Today a large percentage of young adults with clinically primary staphylococcal pneumonia have infections caused by antibiotic-sensitive staphylococci. The mortality did not exceed 10–20% in this group prior to the influenza epidemic

Average age = 36.2 Mortality = 30% Average age = 53.4 Mortality = 92.3%
(From Rogers, D. E.: The current problem of staphylococcal infections. Ann. Int. Med. 45:748, 1956.)

of 1957. In contrast, older patients who acquire staphylococcal pneumonia within the hospital have infections caused by strains resistant to many antistaphylococcal drugs. Mortality is exceptionally high in this group, and between 50 and 90% of these patients succumb despite therapy. Because of the disease setting in which this infection develops, it is often difficult to assign the staphylococcus a primary role as the cause of death (Fig. 3).

It should be emphasized that staphylococcal pneumonia is a disease vastly different from pneumococcal pneumonia. From its inception, staphylococcal pneumonia is a necrotizing, destructive process. Abscesses invariably form. In contrast to the situation in pneumococcal pneumonia, short delays in effective therapy may allow irreversible lung damage to occur. A 24-hour delay in recognizing the staphylococcal pneumonia may make the difference between complete recovery with normal pulmonary function and extensive lung destruction and/or death.

Staphylococcal Bacteremia

Staphylococcal bacteremia is a serious problem in current hospital practice. Not a primary entity, it develops as a secondary phenomenon where local defense mechanisms limiting infection are bypassed. Thus symptoms in a particular patient depend largely on the original source of staphylococci and the site and extent of metastatic infection.

Incidence of staphylococcal bacteremia.—It is widely believed that staphylococcal bacteremia cases are increasing. Nevertheless, recent surveys suggest that the number of patients with staphylococcal bacteremia seen in large hospital centers has remained roughly constant over the past 15–20 years (9, 18–21). Figure 4 shows the incidence of staphylococcal bacteremia seen in 3 large hospitals from 1940 to 1956. These observations suggest a temporary decline in the number of bacteremias observed during 1944–1948 when penicillin was first available in adequate quantities. Since 1950, the number of cases has risen to approximately the same level as that of 1940. In general, 5–15 patients with staphylococcal bacteremia are observed each year in any large medical center.

Analysis of cases observed at The New York Hospital suggests that although the over-all incidence has not changed remarkably, there has been a shift in the type of clinical set-

FIG. 4.—Incidence of staphylococcal bacteremia observed at The New York Hospital (1), Mayo Clinic (2) and Cincinnati General Hospital (3), 1940–1956.

ting in which staphylococcal bacteremia arises. Prior to antimicrobials, bacteremia was more common in infants and children. In this group, bacteremia was seen principally in patients admitted with acute staphylococcal osteomyelitis. Thus in the 3-year period, 1940–1942, 14–17 cases of staphylococcal bacteremia per year were noted on the pediatric service. In contrast, only 1–3 cases of staphylococcal bacteremia were seen in children during 1954–1956. Our figures suggest that increasing numbers of patients in older age groups have developed bacteremia during recent years. In The New York Hospital, the incidence of staphylococcal bacteremia in adults has increased from approximately 3–5 patients per year in 1940–1942 to 5–13 patients per year in the past 3 years. This shift in age group is in part due to the fact that staphylococcal bacteremia is increasingly an intrahospital disease. In virtually all studies, 50–75 per cent of bacteremias seen today arise within the hospital. A disturbing number of these follow relatively minor surgical procedures.

PRIMARY FOCUS.—Studies by Skinner and Keefer performed prior to the use of antimicrobials indicated that cutaneous staphylococcal infections preceded bacteremia in approximately 50% of cases (22). Respiratory infections were the primary focus in 20–25%. Infections of the genitourinary tract were responsible for subsequent bacteremia in 8–10% of cases. In 10% of patients, no primary staphylococcal focus could be discovered.

In current practice, cutaneous infections remain the principal site from which invasion of the blood stream occurs. Postoperative wound infections precede a significant number of bacteremias acquired within hospitals. Relatively minor infections around venous "cut downs" or phlebitis caused by indwelling venous catheters represent primary foci in a number of patients. Genitourinary foci are a more common forerunner of bacteremia than they were in the past. In a recent analysis of 109 cases at the Mayo Clinic, Schirger, Martin, and Nichols report that genitourinary operations preceded bacteremia in 28% of cases (21).

As with other types of staphylococcal infections, serious unassociated disease appears to predispose to bacteremia. This was true before antimicrobials were available, and is especially notable today in older, seriously ill hospitalized patients. Studies by Spink (9), Rogers (19) and Wilson and Hamburger (20) indicate that more than 50% of patients developing bacteremia have advanced debilitating disease.

Staphylococcal bacteremia is a common cause of death in patients with leukemia, metastatic malignancies and congestive heart failure. Patients with exfoliating skin disease or diabetics with extensive vascular complications have a high incidence of staphylococcal sepsis.

CLINICAL MANIFESTATIONS.—In certain patients, staphylococcal bacteremia is a fulminant illness that may run a complete course in 12–24 hours. Much evidence suggests that staphylococcal exotoxin plays a role in this syndrome. Bacteremia may be heralded by the onset of shaking chills, fever of 40–41C., striking tachycardia, cyanosis and rapid vascular collapse. In these patients there is little evidence of metastatic involvement of other organs.

More commonly, the symptoms of staphylococcal bacteremia are slower in onset. A septic-type fever gradually develops. Rigors occur in 40% of patients. Disturbed consciousness, confusion, disorientation or frank psychosis are observed in almost 50% of cases. Common nonspecific gastrointestinal disturbances include anorexia, abdominal pain, nausea, vomiting, and diarrhea. Significant migratory pain in joints and muscles occurs in 10–15% of patients. There may be progressive evidence of focal involvement of many organs. Abscesses form in the lungs, kidneys and bones in a high percentage of patients. Focal involvement of the myocardium, brain, liver, spleen and cutaneous tissues is common.

Staphylococcal bacteremia is generally associated with a leukocytosis of 15,000 to 40,000, with a marked shift to the left in the granulocyte series. Leukopenia is seen, however, in 15–20 per cent of patients with rapidly advancing bacteremia, and the absence of a leukocytosis should not contradict the clinical diagnosis. Anemia develops rapidly in most patients. Albuminuria is common and hematuria is seen in 25–30% of patients without endocardial involvement. Diagnosis is established by culturing staphylococci from the peripheral blood.

Staphylococcal Endocarditis

A significant number of patients with staphylococcal bacteremia develop endocardial involvement. In Skinner and Keefer's series (22), endocarditis developed in 13 of 122 patients (10%). In recent reports the incidence is significantly higher. Thus endocardial involvement was noted in 38 of 109 patients (35%) with staphylococcal bacteremia seen at Johns

Hopkins Hospital between 1933 and 1953 (18). Of 55 patients with staphylococcal sepsis studied from 1940–1955 by Wilson and Hamburger 35, or almost 64%, developed endocarditis (20). Approximately 20% of bacterial endocarditis cases currently seen in The New York Hospital are due to staphylococci. Staphylococci were isolated from less than 10% of cases of proved endocarditis studied by Thayer before antimicrobials were available (23).

TABLE 3.—UNDERLYING HEART DISEASE AND VALVULAR INVOLVEMENT SEEN IN 98 CASES OF STAPHYLOCOCCAL ENDOCARDITIS*

		NUMBER OF PATIENTS
1.	Underlying Heart Disease	53
	Rheumatic heart disease	35
	Congenital heart disease (patent ductus arteriosus, I.V. septal defects predominating)	11
	Arteriosclerotic heart disease	5
	Syphilitic heart disease	2
2.	No Underlying Heart Disease	45
3.	Valves Involved	
	Mitral alone	36
	Aortic alone	17
	Combined mitral and aortic	18
	Tricuspid alone or with other valvular involvement	20†
	Other sites (ductus, I.V. septal defect, left ventricular wall)	8

*From: Fisher *et al.* (18), Wilson and Hamburger (20), and Dowling *et al.* (24).
†Ten cases of tricuspid endocarditis were observed in narcotic addicts.

In contrast to *Streptococcus viridans*, the staphylococcus frequently engrafts on previously undamaged heart valves. There is no history of heart disease in 40–50% of patients who develop staphylococcal endocarditis.

Table 3 summarizes data obtained from 3 large series of patients with endocarditis, reported by Fisher, Wilson, Dowling *et al.* (18, 20, 24). Out of 98 patients, 53 had evidence of previous valvular disease. In 35, rheumatic heart disease was present. In 11 patients, staphylococci engrafted on congenital cardiac lesions, principally I.V. septal defects or a persistent ductus arteriosus. Preceding arteriosclerotic or syphilitic heart disease was noted in 7 patients. Forty-five patients who developed endocarditis had no pre-existing heart disease.

As in other forms of bacterial endocarditis, the mitral valve

is the usual site of infection. Nevertheless, the incidence of aortic valve involvement is significantly higher than it is in streptococcal endocarditis. Thirty-five of the 98 patients had aortic valve lesions alone or associated with mitral-valve lesions. Endocarditis on the right side is more common than in streptococcal disease, partly because of the frequency of staphylococcal involvement of the tricuspid valve in narcotic addicts who administer drugs intravenously.

Figure 5 summarizes the age of onset of staphylococcal endocarditis in 190 patients on whom data are available. The

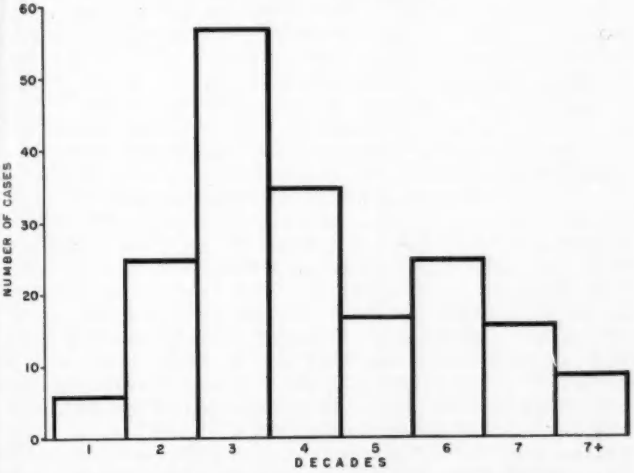

FIG. 5.—Age of onset of staphylococcal endocarditis in 190 patients.

incidence of disease rises, reaching a peak between 30 and 40. A significant number of cases occurs in all subsequent decades, with a secondary peak between 50 to 60. More than 25% of cases occur after 50. Comparison of the age of patients with endocarditis seen before and after the introduction of antimicrobials shows no significant change in age incidence pattern.

Typically, staphylococci produce the clinical picture of acute bacterial endocarditis. Ulcerative, destructive valvular lesions are characteristic, and perforation or rupture of valve

leaflets, valve-ring abscesses and focal myocardial abscesses are common. In the majority of patients, symptoms are identical to those observed in uncomplicated staphylococcal bacteremia. Chills, fever and gastrointestinal symptoms are usual. Arthralgias, without evidence of true joint involvement, are present in about one third of patients. Pulmonary symptoms are noted in patients with tricuspid disease. The central nervous system is often involved during the course of staphylococcal endocarditis. Meningitis or cerebritis occurred in 54% of cases reported by Wilson and Hamburger (20).

Because of the acute and relatively rapid course of the illness, peripheral embolic phenomena are less common than in streptococcal endocarditis. Splenic enlargement occurs in approximately 20% of patients. Roughly 40% of patients develop cutaneous manifestations during the course of the disease. Petechial lesions of the skin and mucous membranes are most common. Erythematous rashes, often associated with petechiae or frank purpura, are occasionally seen. Typical Osler nodes are found in less than 10% of patients. In 10–15% of cases pustular skin and subcutaneous lesions occur. These should always suggest staphylococcal endocarditis.

In each series reported it is noted that 10–15% of patients with staphylococcal endocarditis run a prolonged subacute clinical course indistinguishable from that seen in streptococcal endocarditis. Figure 6 illustrates the hospital course of a patient with subacute *Staphylococcus aureus* endocarditis. Symptoms were present for a year before diagnosis was established. In such patients, the classic peripheral signs of bacterial endocarditis (i.e., petechiae, splinter hemorrhages, hematuria, palpable spleen) are more commonly found.

Coagulase-positive hemolytic *Staphylococcus aureus* strains are cultured from 80–85% of patients with staphylococcal endocarditis. Coagulase-negative *Staphylococcus albus* strains are responsible for 15–20% of cases. This fact should be remembered in dealing with a patient whose symptoms suggest bacterial endocarditis when blood cultures are reported as "contaminated" with *Staphylococcus albus*.

It is my impression that patients infected with coagulase-negative strains are more likely to run a subacute course. Studies by Dowling and his associates do not reveal differences in valve predilection or outcome with coagulase-positive or coagulase-negative strains (24).

Two rather unusual conditions in which staphylococcal endocarditis has arisen should be noted. First, staphylococci

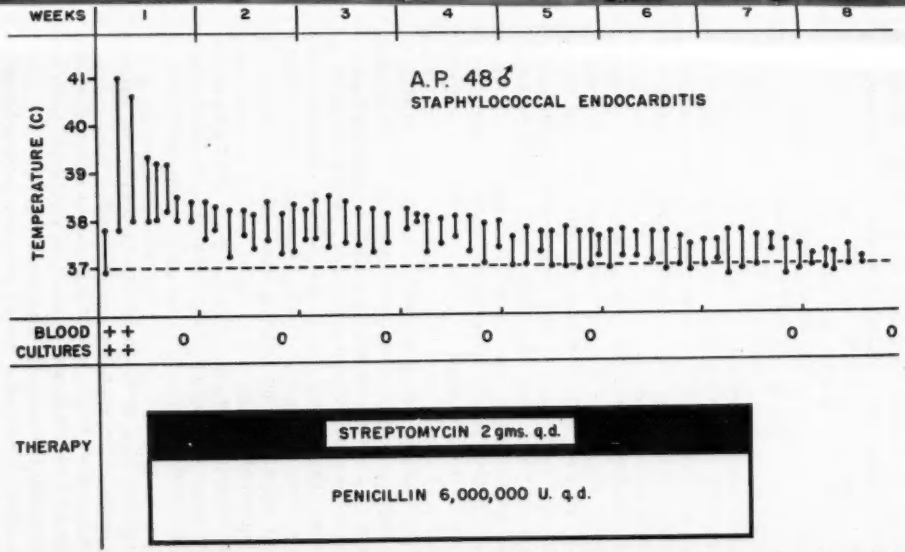

FIG. 6.—Male, 48, with rheumatic heart disease, admitted with subacute bacterial endocarditis of 1 year's duration. Patient had repeatedly self-administered oral penicillin, always experiencing prompt defervescence and loss of symptomatology lasting several days. Four consecutive blood cultures were positive for a coagulase-positive *Staphylococcus aureus* which was sensitive to 0.05 units of penicillin and 0.2 micrograms of streptomycin per ml. Two features are noteworthy: the penicillin sensitivity of the microorganism despite repeated suboptimal administration of penicillin, and the extremely slow temperature response to appropriate therapy.

(or monilia) have been common etiologic agents in the endocarditis occurring in narcotic addicts who self-administer drugs intravenously. In this group, tricuspid involvement is common and pulmonary symptoms of cough, occasional hemoptysis and right-sided failure are the rule.

Secondly, with advances in cardiac surgery, it has become apparent that bacterial endocarditis occasionally follows intracardiac operations and is probably causally related to the operative procedure. I am aware of 67 such cases. Staphylococci have been the etiologic agent in 11 of 20 cases in which the infecting microorganism has been reported. (Again, monilia have been common.) Six cases have been caused by coagulase-negative *Staphylococcus albus* strains, 5 by coagulase-positive *Staphylococcus aureus* strains. Of interest is the fact that virtually all postoperative endocarditis caused by *Staphylococcus albus* (5 of 6 cases) has followed finger fracture of the aortic valve, and infection has occurred at the operative site. All postoperative cases of *Staphylococcus aureus* endocarditis have followed finger fracture of the mitral valve. All *Staphylococcus aureus* strains have been resistant to many antibiotics. Whether this difference in valve predilection is fortuitous or of real biologic significance remains to be determined.

Laboratory findings are not specific with endocardial involvement. Persistently positive blood cultures are highly suggestive, particularly when similar numbers of microorganisms appear in each specimen. Leukocytosis of 10,000 to 15,000 is present in more than 75% of patients. Almost all patients develop anemia. Hematuria is common. More than three fourths of patients have red blood cells in the urine at some time during the course of illness.

The destructive nature of the valvular involvement makes early recognition extremely important. Three facts about staphylococcal endocarditis can be used constructively in diagnosis:

1. The incidence of valve involvement is high in patients with staphylococcal bacteremia (10–60% of cases).

2. Bacterial endocarditis is found in the autopsy of almost every patient with staphylococcal bacteremia who has clinical evidence of significant valvular disease.

3. Skin lesions (petechiae, multiple cutaneous abscesses, erythematous rashes) are unusual in staphylococcal bacteremia unless endocarditis is present.

It thus seems reasonable to assume that endocarditis is present in any patient with staphylococcal bacteremia who has clinical evidence of valvular disease and/or skin manifestations, and, in consideration of this, treatment should be begun accordingly.

PROGNOSIS IN STAPHYLOCOCCAL BACTEREMIA AND ENDOCARDITIS

Mortality in staphylococcal bacteremia with or without endocardial involvement has remained high. Prior to the introduction of antimicrobial drugs, 75–85% of these patients died. Staphylococcal endocarditis was invariably fatal. In the mid 1940's, when penicillin was first available in adequate quantities, successful cure of 72% of 28 patients with staphylococcal bacteremia was reported by Hall and Spink (25). In recent years, mortality in adequately treated patients has ranged from 35–70% in different series.

Most reports suggest that the presence of endocardial involvement reduces only slightly the chances of survival. Fifty-seven of the 98 patients with staphylococcal endocarditis reported by Dowling *et al.* received antimicrobial therapy. Twenty-eight, or approximately 50%, of these patients recovered. Spink's recent experience stands in contrast. Of 17 patients with staphylococcal endocarditis treated in the University of Minnesota hospitals during the period 1949-1955, only 1 recovered (9).

In common with other staphylococcal infections, the incidence of bacteremia due to microorganisms not susceptible to many antistaphylococcal agents has risen steadily. This phenomenon is commonly advanced as the reason for the continuing high mortality. It appears probable, however, that the problem is more complex. Clearly many patients developing staphylococcal bacteremia are significantly older and are more seriously ill with other associated disease than in the past. In my experience and that of Knight and Collins (26), it is rare to see a bacteremia in which the staphylococcus isolated was not susceptible to at least 1 effective antistaphylococcal drug. Antibiotic susceptibility and survival have not correlated well. In many patients already precariously ill, the emergence of any staphylococcal infection is the final insult and therapy, regardless of its speed or adequacy, does not alter the outcome.

Postoperative Staphylococcal Infections

Only a few surgical clinics have made careful studies of the current incidence of postoperative infections. Nevertheless, it is generally agreed that an increasing number of infections caused by staphylococci have been noted on virtually every surgical service checked. Reasons for this intrahospital problem are fourfold:

1. Advances in anesthetic and surgical technics now allow extensive surgery on older and more seriously ill patients than in the past. These patients are more susceptible to staphylococcal infections.

2. Hospital and surgical personnel show a high staphylococcus carrier rate, and surgical amphitheaters are almost invariably contaminated with antibiotic-resistant staphylococci. Blankets, mattresses and articles of clothing in contact with patients and their open wounds have been repeatedly shown to harbor potentially virulent antimicrobial-resistant staphylococci.

3. Patients undergoing surgery are commonly put on prophylactic antimicrobial agents. As has been indicated, such prophylaxis seems to eradicate sensitive strains of staphylococci in normal carriers but may increase the acquisition of antibiotic-resistant staphylococci.

4. It has been tacitly, but erroneously, believed that antimicrobial therapy can substitute for occasional breaks in tedious aseptic technics in preventing subsequent infection.

In well-managed surgical units, an incidence of postoperative wound infections in excess of 2% was generally considered unacceptable in the decade preceding antibiotics. In recent studies by Howe (27), and Blowers *et al.* (28), infection rates of 4 or 5% have been noted on excellent surgical units. Infection rates as high as 10%, indeed, as high as 37%, have been reported (29).

The majority of postoperative infections consist of simple cutaneous abscesses occurring at the operative site. Nevertheless, bacteremia, metastatic spread and death have occurred in some patients. Postsurgical staphylococcal infections have been particularly troublesome in thoracic surgery units, with chest cavity involvement and empyema frequent.

In some instances it has been possible by phage-typing technics to demonstrate that a series of infections has stemmed from one patient. This observation again suggests that certain strains of staphylococci may be peculiarly prone

to cause intrahospital infection. Possible approaches to this problem will be discussed in the section on prevention and prophylaxis.

STAPHYLOCOCCAL ENTEROCOLITIS.—Staphylococcal enteritis, or enterocolitis, is a clinical syndrome characterized by nausea, vomiting, diarrhea, peripheral vascular collapse, and a significant fatality rate. Recently this syndrome has been recognized as an occasional complication of broad-spectrum antimicrobial therapy (30). Certain other factors, including abdominal surgery, episodes of hypotension and poor oral food intake may play a part in its pathogenesis. Staphylococcal enterocolitis has appeared most commonly on surgical units in patients receiving oral broad-spectrum antibiotics, but also has been noted following the parenteral use of antibiotics such as penicillin and streptomycin which have broad-spectrum activity.

Typically, staphylococcal enterocolitis has occurred in elderly surgical patients receiving broad-spectrum antibiotic therapy. Initial symptoms are usually anorexia and ill-defined feelings of general malaise. These symptoms are rapidly followed by a rising temperature and diarrhea. Nausea and vomiting are common. Because of reduction in fecal mass (antibiotics and poor oral intake) the severity of the diarrhea is frequently unrecognized. Nevertheless, large amounts of fluid are lost in small, frequent stools. Excessive dehydration and hemoconcentration may occur; and this illness may be rapid and fatal in older patients.

Stool specimens may resemble staphylococcal pus associated with blood and pseudomembranous casts of the gut. Stool smears show masses of Gram-positive cocci and polymorphonuclear leukocytes. Cultures reveal coagulase-positive staphylococci in large numbers or in pure culture that are resistant to the antimicrobials in use. Staphylococci isolated from patients with enterocolitis produce enterotoxin.

Changes in the bowel noted at autopsy have ranged from insignificant mucosal lesions to complete replacement of mucosal lining by a pseudomembrane composed of mucus, leukocytes and fibrin. Microscopic examination may show mucosal destruction, polymorphonuclear infiltration and masses of Gram-positive cocci lying within the submucosa.

It should be noted that not all postantibiotic diarrheas are staphylococcal in origin. In some patients with acute colitis, and pseudomembrane formation, no staphylococci have been recovered on culture or at autopsy.

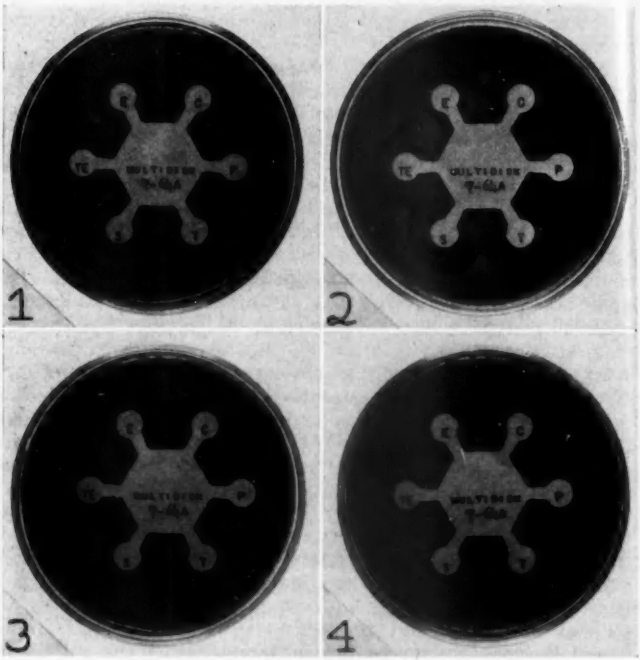

FIG. 7.—Sensitivity patterns of 4 strains of staphylococci. E = erythromycin, C = chloramphenicol, P = penicillin, T = tetracycline, S = streptomycin, TE = oxytetracycline. Disks 1 and 2 show a *Staphylococcus aureus* strain isolated from outpatients, disk 3 a typical intrahospital staphylococcus and disk 4 a staphylococcus susceptible only to chloramphenicol.

DIAGNOSIS OF STAPHYLOCOCCAL INFECTIONS

THE CLINICIAN VERSUS THE LABORATORY

Our inability to make swift bacteriologic diagnoses in the laboratory constitutes one of the major problems in the treatment of staphylococcal infections today. The specific identification of staphylococci is based on the visible growth of micro-

organisms on bacteriologic media. Such growth requires 8–48 hours. Because of the necrotizing destructive nature of most staphylococcal infections, therapy, to be truly effective, must be started well before such laboratory information is available.

It is thus apparent that the diagnosis of staphylococcal disease and initial decisions regarding appropriate therapy must of necessity be *clinical*. Staphylococcal pneumonia must be suspected in the hospitalized patient who suddenly develops high fever, cough and a pulmonary infiltrate. Staphylococcal bacteremia should be considered in patients with exfoliating skin disease who develop spiking temperatures and evidence of sepsis during hospitalization. Patients with agranulocytosis or leukemia who develop rapidly advancing pustular skin lesions must be started on treatment promptly.

The laboratory plays an essential *secondary* role. Bacteriologic facilities for the isolation of staphylococci, coagulase testing of isolates and simple sensitivity studies are now necessary for intelligent treatment of virtually all intrahospital staphylococcal infections. Phage typing is required for the precise identification of individual strains, but technics are cumbersome, requiring specially trained personnel.

ISOLATION OF STAPHYLOCOCCI.—Staphylococci are readily cultured on all simple laboratory media. They are readily identified as surface colonies on blood agar plates incubated aerobically at 37C. Sheep's blood is preferable, but outdated human blood or rabbit blood is almost equally acceptable. Most pathogenic *Staphylococcus aureus* strains grow rapidly, producing round, smooth, opaque yellow colonies within 8–24 hours on blood agar plates. The majority produce a clear surrounding zone of hemolysis. Pigment production can be seen more readily on colorless agar slants stored at room temperature. Strains of *Staphylococcus albus* are nonhemolytic, produce opaque white colonies, and are generally somewhat slower growing.

THE COAGULASE TEST.—The most valuable method for differentiation of saprophytic from pathogenic strains of staphylococci is the coagulase test. In our laboratory this is performed by the tube method. One-half cc. of a 1–10 dilution of human or rabbit plasma in saline is placed in a sterile test tube. A few drops of an overnight culture or a small loopful from a colony on solid media is placed in the plasma and the tube incubated at 37C. Tubes are examined for the presence of a clot at 4 and at 24 hours. Coagulase-positive strains produce an opaque clot. A more rapid slide-test method which

gives a good correlation with the tube method also may be used (31).

ANTIBIOTIC SENSITIVITY STUDIES.—Accurate information regarding the antibiotic susceptibility of the strain isolated is necessary in the treatment of staphylococcal infections. It is our practice to use the "disk" method for preliminary information in a large number of staphylococcal infections because of the speed and simplicity of this procedure. The surface of a blood-agar plate is heavily streaked from an overnight infusion-broth culture or from a saline emulsion prepared directly from a discrete surface colony of staphylococci. Commercial disks containing appropriate quantities of antimicrobials are immediately placed on the plate surface and the plate incubated at 37C. Readings are taken at intervals from 8–24 hours. Typical plates prepared this way with a convenient multidisk containing 6 antibiotics are shown in Figure 7.

We have found the correlation between disk and tube dilution tests to be excellent for most antimicrobials tested except penicillin. Because of limitations in dose, serum levels that can be attained with most antibiotics fall within a relatively narrow zone. Thus the quantity of drugs contained in disks can be adjusted to indicate "resistance" at levels commonly attained in body fluids. Penicillin dosage can be varied widely and serum levels of 1 unit to 100 units can be maintained. Thus, resistance to penicillin is relative, and precise quantitative information becomes important in determining therapy.

Virtually all of staphylococci isolated from serious infections are subsequently subjected to tube-dilution sensitivity studies. This method has the advantage of indicating more precisely the drug levels necessary to inhibit staphylococcal growth. It has the disadvantages of requiring a pure culture obtained from the original plates, 12 to 15 test tubes for each drug under study, and laboratory personnel with sufficient time and technical experience to perform the test.

BACTERIOPHAGE TYPING OF STAPHYLOCOCCI.—The use of a series of lysogenic staphylococcal bacteriophages now allows more precise identification of individual strains of staphylococci. Although not a procedure which can be easily maintained in a routine diagnostic laboratory, phage typing permits more precise analysis of the epidemiology of staphylococcal infections and the staphylococcal carrier state.

In most laboratories where phage typing is done, 25–28 staphylococcal phages are maintained (32). Between 40 and

70% of coagulase-positive staphylococci can be characterized by different lysis patterns using the phages currently employed. Coagulase-negative strains are not susceptible to lysis.

Three large phage groups are currently recognized with considerable overlapping of individual strains within each group. In general, hospital strains of antibiotic-resistant staphylococci fall into phage group III. Staphylococci isolated from nonhospitalized people are more commonly strains of phage group II or I. Antibiotic-resistant strains are least common in group II.

TREATMENT OF STAPHYLOCOCCAL INFECTIONS

General Considerations

Certain characteristics of staphylococcal infections bear emphasis in considering specific therapy. These are:

1. Staphylococcal infections characteristically produce rapid necrosis and tissue death at sites of local infection. Clinical and experimental experience suggests that even short delays in therapy may allow an acute reversible infection to become a chronic suppurative process which responds slowly, if at all, to antibiotic drugs.

2. Abscess formation is the rule in staphylococcal infection. Staphylococci residing in such local foci are virtually insusceptible to killing by antibiotic drugs, and surgical drainage of local necrotic lesions plays an extremely important role in management.

3. Staphylococci are killed slowly under even the most optimal antibiotic regimens. As these infections tend to become chronic and the relapse rate is high, therapy must be prolonged.

4. Changing patterns of antimicrobial susceptibility make in vitro sensitivity studies of great importance in determining optimal drug therapy for patients with serious staphylococcal infection. Although therapy must generally be initiated on the basis of previous knowledge of staphylococcal strains prevalent in the community, subsequent alterations in therapy should be based on laboratory study of the microorganism involved.

It is clear that antibiotics alone are rarely, if ever, capable of eradicating microorganisms from the animal body. Nevertheless, it is my belief that staphylococcal infections tend to respond more adequately to "bactericidal" antibiotics than to

"bacteriostatic" antimicrobials. Penicillin, streptomycin, and bacitracin are "bactericidal" agents.

It is now common practice to administer more than 1 antibiotic drug to patients with staphylococcal infections. Indeed, this practice has become so widespread that the possibility of single-drug therapy in staphylococcal infections is rarely considered. Combined antibiotic treatment evolved from multiple considerations:

1. Evidence obtained in the treatment of other infections, notably enterococcal endocarditis and brucellosis, suggests that combined therapy can reduce the incidence of relapse and result in a higher rate of cure in these infections.

(It is important to note that no such evidence is available for response of staphylococcal infections to multidrug therapy.)

2. Staphylococci may develop resistance in vivo to certain antimicrobial drugs when used singly. Increasing resistance of an infection-producing strain has been noted during single drug treatment with streptomycin, erythromycin, and novobiocin.

(It is worth stressing, however, that this phenomena has *not* been seen in the penicillin treatment of penicillin-sensitive staphylococcal infections. In other words, staphylococcal infections which are penicillin-sensitive at their outset almost always remain penicillin-sensitive during therapy.)

3. The unsatisfactory nature of antistaphylococcal therapy in many infections and the uncertainties as to the susceptibility of any given strain to a single antibiotic agent make most physicians unwilling to risk single-drug therapy with what may prove an ineffective agent after sensitivity studies are available.

Thus, although there is no solid evidence to prove that multiple drug therapy of staphylococcal infections is more efficacious than single drug therapy, virtually all clinicians are now using multiple drug regimens.

Antimicrobial Drugs Used in Treatment

Penicillin, streptomycin, erythromycin, chloramphenicol, novobiocin, the tetracyclines and bacitracin have been used alone or in different combinations in the treatment of staphylococcal infections.

Penicillin.—Penicillin is universally agreed to be the agent of choice in treating penicillin-sensitive staphylococcal

infections. Current evidence suggests that blood levels should be continuously maintained throughout each 24-hour period. Aqueous crystalline penicillin G administered every 4 hours is probably preferable to longer-acting repository forms of penicillin. Total daily doses of 2 million to 6 million units generally give adequate serum levels for treating infections caused by strains sensitive to less than 0.5 units per ml.

Although opinion is divided on this point, certain clinicians, including the author, believe that some staphylococcal infections caused by strains ordinarily considered "resistant" to penicillin (1 to 50 units per ml.) respond to large doses of penicillin (10 million to 100 million units per day).

The nature of staphylococcal penicillin resistance suggests that such treatment may be reasonable. Penicillin-resistant staphylococci elaborate an enzyme, penicillinase, which inactivates the drug when large numbers of staphylococci are grown in vitro. Nevertheless, individual staphylococcal cells are sensitive to penicillin. It seems improbable that penicillin can materially affect established staphylococcal lesions where there are large numbers of organisms and high local concentrations of penicillinase. Nevertheless, it seems likely that penicillin can effectively attack individual penicillin-sensitive cells, or small numbers of cocci, when they enter the blood stream and thus may prevent extension or metastatic spread.

There is general agreement that staphylococcal infections caused by strains of high penicillin resistance (over 100 units per ml.) rarely, if ever, respond to penicillin treatment alone.

STREPTOMYCIN.—Streptomycin and dihydrostreptomycin are excellent antistaphylococcal agents. There are some indications that streptomycin is more active against sluggish, slowly multiplying cells than are other antibiotics. This makes it a good agent for use in managing abscess-producing infection.

Streptomycin may be given intramuscularly every 6–12 hours, using total daily doses of 2 Gm. This dosage must be decreased to 1 Gm. or less daily within 10 days to 2 weeks, to prevent vestibular or auditory nerve damage. We frequently give one half dose as streptomycin, one half dose as dihydrostreptomycin because of the evidence suggesting lower ototoxicity with this combination. Streptomycin should be used cautiously in older patients and in the presence of renal disease.

Because staphylococcal infections due to microorganisms of high streptomycin resistance are on the increase, strepto-

mycin is less commonly used today in the initial treatment of staphylococcal infections. However, where the isolated staphylococcus is shown to be streptomycin susceptible, we believe that this drug is one of the best antistaphylococcal agents available.

ERYTHROMYCIN.—This agent has proved extremely valuable in the management of staphylococcal infections. In our community, approximately 80% of staphylococci producing intrahospital infections are susceptible to erythromycin. It may be administered orally every 4–6 hours, using doses of 2–6 Gm. daily. It may be given intravenously, 1–2 Gm. daily in divided intravenous infusions. Gastrointestinal symptoms arise in approximately 5% of patients. Side effects are uncommon. Sensitivity reactions are rare.

CHLORAMPHENICOL.—Virtually all staphylococci in our medical community are relatively sensitive to chloramphenicol. This drug is used frequently in treating intrahospital staphylococcal infections. Doses of 2–4 Gm. are given daily by mouth. Preparations are available for intravenous or intramuscular administration of chloramphenicol. Aplastic anemia and agranulocytosis have occasionally occurred following the use of this agent.

NOVOBIOCIN.—The majority of current strains of staphylococci are sensitive to novobiocin. This drug is an effective antistaphylococcal agent. It is almost completely absorbed from the gastrointestinal tract. It should be given in doses of 2 Gm. daily, ½ Gm. every 6 hours, and may be given in similar doses by the intravenous route. Fever and a morbilliform drug reaction occur in 3–10% of patients treated. Certain patients develop a yellowish tint to the skin and sclera, apparently as a result of the metabolic breakdown products of the drug rather than from hepatic damage or bilirubinemia. We have had 1 patient develop agranulocytosis while receiving novobiocin.

THE TETRACYCLINES.—Thirty to 80% of staphylococci isolated in medical practice within the United States are currently sensitive to tetracyclines. Although some strains vary in susceptibility to chlortetracycline, oxytetracycline and tetracycline, these antibiotics can be considered generally as interchangeable. When used, they should be given in oral doses of 2–6 Gm. daily in divided doses or parenterally in doses of 1–2 Gm. Gastrointestinal symptoms of diarrhea, nausea, or vomiting occur in 5–10% of cases.

BACITRACIN.—Bacitracin has proved most effective for

treating certain staphylococcal infections not susceptible to other antibiotics. Most staphylococci are sensitive to bacitracin and its use is increasing in some clinics. It may be administered intramuscularly every 6 hours in doses below 100,000 units daily. Evidences of renal toxicity often develop at higher dosage levels. Virtually all patients develop albuminuria, but this frequently clears, despite continuation of the drug. The high incidence of staphylococcal infections in patients with associated or pre-existing renal damage has narrowed the potential use of bacitracin.

OTHER ANTIBIOTICS.—Two new antimicrobial agents, vancomycin and ristocetin, offer promise as antistaphylococcal agents. They are not yet released for general use, and experiments to date are so limited that conclusions as to their efficacy are unwarranted.

SPECIFIC ANTIBIOTIC THERAPY

The clinical setting in which a staphylococcal infection occurs is of great importance in deciding appropriate initial antimicrobial therapy. If a typical acute staphylococcal infection arises *outside* the hospital in a patient without recent medical or surgical experience, it is appropriate to assume that the microorganism involved is penicillin sensitive. If the infection occurs in a *hospitalized* patient, it should be considered due to a staphylococcus not susceptible to penicillin, streptomycin, and the tetracyclines, unless laboratory evidence to the contrary is obtained. These two situations will be considered separately.

PENICILLIN-SENSITIVE STAPHYLOCOCCAL INFECTIONS.—If systemic staphylococcal infection is assumed to be penicillin-sensitive, appropriate cultures should be obtained and treatment started with 500,000 to 1 million units of aqueous penicillin G administered intramuscularly every 4 hours. Treatment should be continued for a minimum of 4 weeks. In many instances, antibiotics should be administered for 6 weeks to 3 months, particularly if there is evidence of inapproachable abscess formation in the lungs or internal organs. If endocardial involvement is suspected, maximal therapy should be continued for at least 6–8 weeks. Where response is prompt and intravascular infection is not present, it is reasonable to modify the antibiotic regimen in 2–3 weeks, switching to procaine penicillin, 600,000 to 1 million units every 12 hours for the remaining period of therapy. The

patient should be re-examined often to detect whether surgically approachable abscesses have arisen, and local surgical drainage should be carried out wherever possible.

Many physicians routinely use a companion antimicrobial in treating penicillin-sensitive staphylococcal infections, although the value of combined therapy in such cases is uncertain. Streptomycin, erythromycin, chloramphenicol, or novobiocin are the usual companion drugs. In general, staphylococci sensitive to penicillin are also susceptible to all other antistaphylococcal agents.

PENICILLIN-RESISTANT STAPHYLOCOCCAL INFECTIONS.—Treatment of antimicrobial-resistant staphylococcal infections is currently unsatisfactory. Different regimens have been proposed, but these appropriately vary, depending on the characteristics of the strains of staphylococci most prevalent in a given setting. The two regimens outlined here are in use. Most clinicians widely experienced in managing staphylococcal infections currently use regimen 1. A smaller number of physicians continue to use regimen 2 in some intrahospital infections.

1. *Initiation of therapy with two antimicrobial agents other than penicillin.*—In most medical centers, erythromycin and chloramphenicol are initially used together in full doses whenever a penicillin-resistant staphylococcal infection is suspected. Where these drugs can be given orally, they are administered in doses of 2–6 Gm. daily on a divided schedule, 0.5–1.0 Gm. every 4–6 hours. If parenteral drug therapy is required, 1–3 Gm. of erythromycin and 1–2 Gm. of chloramphenicol may be administered daily in divided intravenous infusions. Chloramphenicol can be administered in 6–12 hourly intramuscular injections. Again, maximal therapy should be maintained for long periods in most systemic infections.

In certain hospitals, the increased incidence of erythromycin-resistant strains has led to the substitution of novobiocin in the initial treatment regimen.

2. *Initiation of therapy with penicillin and a companion antimicrobial drug.*—In treating a number of patients suspected of harboring penicillin-resistant staphylococcal infections, it is our practice to start with large doses of aqueous penicillin G together with a companion antistaphylococcal drug. Penicillin is administered 10–20 million units a day in divided 2–4 hourly intramuscular injections by continuous intravenous infusion. The antibiotics currently used as com-

panion drugs at The New York Hospital are erythromycin, chloramphenicol, streptomycin and novobiocin.

Alterations in Therapy During Course of Infection

A number of staphylococcal infections do not respond satisfactorily to the regimens outlined. When should therapy be altered? This is one of the most difficult decisions to make in treating serious staphylococcal disease.

Staphylococcal infections respond slowly even to the most effective antimicrobial regimens. In many instances, the therapeutic response resembles the response of typhoid fever treated with chloramphenicol. It is not uncommon for fever to remain relatively unchanged for 24–48 hours after the initiation of effective therapy. The temperature then gradually falls by lysis over 7–14 days. Figure 8 shows the typical temperature response to effective antimicrobial therapy, as illustrated by a young woman with *Staphylococcus aureus* pneumonia. This slow temperature response should be kept in mind in deciding the efficacy of any given regimen.

Laboratory studies on the strain involved should aid in but not dictate alterations in therapy. If the clinical response appears adequate, with no evidence of further extension of infection and if there is a gradual decline in temperature, it is often advantageous to continue with initial therapy even in the face of laboratory evidence suggesting resistance to the drugs being used. If, however, there is evidence that the disease is progressing beyond a 48-hour period, or if the infection advances rapidly during the first 24–48-hour period, antibiotic therapy should be shifted, or new antibiotic agents added, using in vitro sensitivity studies as a guide to choice of drugs.

Surgical Therapy

After an abscess has formed, staphylococcal infections are extremely difficult to eradicate without proper external drainage. Staphylococcal empyema almost universally requires surgical intervention. Carbuncles and boils, after they have localized, are better handled surgically than with antimicrobials. Obviously, many staphylococcal infections do not focalize in areas amenable to surgical drainage, but this possi-

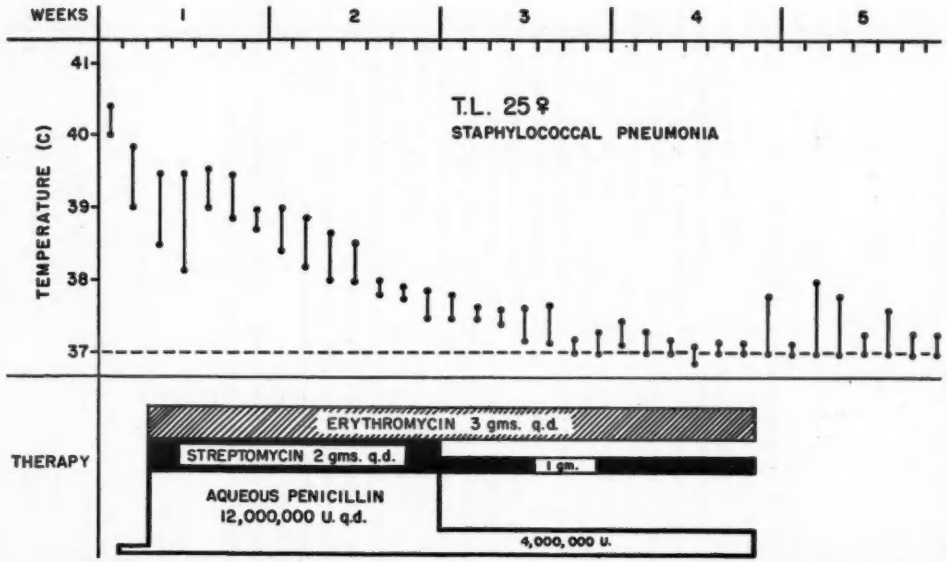

FIG. 8.—Female, 25, hospitalized with staphylococcal pneumonia of the right middle and lower lobes which followed an influenza-like illness. The staphylococcus isolated was resistant to penicillin but highly sensitive to erythromycin and streptomycin. Note the extremely slow temperature response to appropriate antibiotic therapy.

highly sensitive to erythromycin and streptomycin. Note the extremely slow temperature response to appropriate antibiotic therapy.

bility should be reviewed in any patient with an unsatisfactory therapeutic response.

Special Therapeutic Problems

1. *Superficial infections.*—Simple superficial infections do not necessarily require the use of antistaphylococcal drugs. Once a frank abscess is formed, antibiotics do little to modify the local lesion, although they may prevent secondary superficial lesions or blood stream invasion. If given early, any antistaphylococcal drug may abort the full development of a boil or carbuncle. If superficial infections are widespread or recurrent, it is probably worthwhile to attempt antimicrobial therapy. Antibiotic drugs should be administered in full doses and continued for a minimum of 10–14 days. These should be used along with local moist heat, immobilization of the affected part, if possible, and local surgical therapy. Manipulation and surgical intervention should be avoided until clear suppuration occurs. Moist heat should be discontinued when surgical or spontaneous drainage ensues, to prevent maceration of surrounding skin and satellite seeding of lesions. The surrounding skin can be protected with a coating of zinc oxide.

It has been demonstrated that virtually all patients who have recurrent episodes of local staphylococcal infection are persistent nasal carriers of the same strain. Although the evidence as to efficacy is not available, it may be worthwhile to attempt to eliminate the nasal-carrier state by locally instilling a topical antibiotic not in general systemic use. We have used bacitracin ointment of the anterior nares, but whether this has modified the course of cutaneous disease is questionable.

2. *Acute osteomyelitis.*—Acute osteomyelitis in young people is almost invariably caused by penicillin-sensitive staphylococci, although we have encountered a case in the past two years that was due to a typical hospital strain. With most patients, aqueous penicillin, 300,000–500,000 units every 2–4 hours, is appropriate therapy. This should be continued 3–4 weeks. It is rare that surgical intervention is required in the current management of osteomyelitis, and surgery should probably be withheld unless a frank subcutaneous abscess forms. If the disease is promptly diagnosed and treated, chronic osteomyelitis with sequestra rarely occurs and recovery is complete and lasting. If an antibiotic-resistant strain is

suspected, erythromycin, novobiocin, or chloramphenicol should be administered along with penicillin.

3. *Staphylococcal enterocolitis.*—Treatment of staphylococcal enterocolitis consists of prompt discontinuance of antibiotics, careful fluid and electrolyte replacement, together with the administration of a different antimicrobial predictably active against most strains of resistant "hospital" staphylococci. Erythromycin has been the drug of choice in most institutions. The increased incidence of erythromycin-resistant strains of staphylococci has led to the use of novobiocin in certain patients, with good results.

Profound fluid loss and, perhaps, exotoxin absorption seem to be the principal causes of death in this disease. Infection generally remains limited to the gastrointestinal tract. Administration of ACTH or one of the corticosteroids has been suggested in fulminant cases in conjunction with treatment already outlined. Although the rationale appears sound, we have had no experience with this regimen.

PREVENTION OF STAPHYLOCOCCAL INFECTIONS

Clinical experience indicates that staphylococcal infections, once established, will continue for the present to cause mortality in hospitalized patients. Epidemics of staphylococcal infections in the newborn and in postpartum mothers as well as postoperative staphylococcal infections are a serious recurring problem in many hospitals. It is clear that this situation has been caused, in part, by the very antimicrobial drugs that have produced such an immense decline in the morbidity and mortality of acute bacterial infections. The present hospital staphylococcal problem is analogous on a small scale to the problem of streptococcal puerperal sepsis faced by Semmelweis and Oliver Wendell Holmes during the middle nineteenth century.

In the past 20 years, the therapy of established staphylococcal infections has received major investigative emphasis. Now we must explore technics for preventing staphylococcal infection with the same experimental thoroughness. As new medical and surgical therapies prolong life and allow abnormal, altered hosts to survive, it seems probable that the problem of staphylococcal infection will increase.

Recognizing the gaps in current knowledge regarding the transmission of staphylococci within hospitals or the precise nature of the susceptible host, some rules for preventing

staphylococcal infections in hospitals can be set forth arbitrarily. It seems probable that further experimental work will help to establish more effective prevention.

1. All hospital personnel should be made aware of their own staphylococcal-carrier state and the potential hazard it represents to patients. The increased rather than decreased need for common-sense personal hygiene and cleanliness should be firmly ingrained in all who have contact with patients. Because of evidence suggesting that an individual with an active staphylococcal infection is a more serious potential threat to debilitated patients, personnel with cutaneous staphylococcal lesions should be relieved of duties, whenever possible.

2. The advisability of hospitalizing certain patients known to be highly susceptible to staphylococcal disease should receive more serious consideration. Many of us have had the unfortunate experience of seeing patients with long-standing granulocytopenia or exfoliative skin disease hospitalized only to develop serious staphylococcal sepsis. In our current state of ignorance this hazard should be recognized, and many of these patients should be treated at home rather than subjecting them to the high concentrations of antibiotic-resistant staphylococci now prevalent in hospitals.

3. Wherever practical, patients of known high susceptibility to staphylococcal infection should be isolated. Ideally this would include many debilitated patients, those with denuding skin disease, those with diseases of the bone marrow or of the reticuloendothelial system and patients in a coma from any cause. Nurseries for the newborn need redesigning for effective separation of infants to prevent cross-contaminating aerosols. In certain hospitals, infant infections have been significantly reduced by instituting "rooming in" for newborns, to prevent contact with other infants. The large ward should be replaced by smaller 2–4 bed units on medical and surgical services, with ample space between beds.

4. Antibiotic drugs should be used more cautiously in prophylaxis. Current evidence suggests that antibiotic prophylaxis is a mixed blessing except in relatively specific and well-defined situations. Often antibiotics prevent pneumococcal or streptococcal infections only to allow staphylococcal infections to supervene. The routine use of prophylactic antibiotics, particularly prevalent on surgical services, probably should be abandoned. Current studies suggest that a reduction

in the carrier state in personnel may follow curtailment of antibiotic agents for prophylaxis.

5. It has been recognized that many postoperative infections on surgical units arise within the operating room. The number of personnel entering an operating theater should be restricted sharply and motion within the room planned and limited. Certain more specific procedures recommended by Howe (27) and Starkey (33) should be studied on other surgical services. These include: (a) double masking of operating room personnel and changing of masks every 1–2 hours during long operations, to prevent saturation and discharge of staphylococci; (b) complete masking, gowning and gloving while changing septic dressings; (c) use of special, separately maintained septic sets for managing infected wounds; (d) isolation of patients with wound infections, and the use of occlusive wound dressings for patients in whom isolation is impractical.

6. In this era of new synthetic fabrics, such items as the wool blanket and feather pillow should probably be eliminated from hospitals. Bedding that can be laundered and sterilized often without damage should be substituted. Nonporous pillow and mattress covers should be changed with each occupant.

7. Physicians should be aware of the significant incidence of infection following certain minor therapeutic procedures. Repeated aspirations of the pharynx, or the tracheobronchial tree via tracheotomy, with unsterile rubber catheters should be reconsidered. Continuous infusions through venous cut downs or with plastic catheters should be used sparingly. Catheterization of the bladder should require definite major indications for its use.

Studies to date suggest that the procedures outlined will not solve the problem of staphylococcal infection. None of the above suggestions deals directly with the primary problem: that of the *altered, susceptible human host.* Studies on factors that characterize host susceptibility are now in progress in certain laboratories. Future hope of control of staphylococcal disease seems to lie in therapy directed toward the "susceptible" state in hospitalized patients rather than in the treatment of established infection.

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